

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209905Orig1s000

PRODUCT QUALITY REVIEW(S)



Recommendation: Approval

**NDA 209905
Review #1**

Drug Name/Dosage Form	Amphetamine Sulfate Orally Disintegrating Tablets
Strength	5, 10, 15, 20, (b) (4) mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Arbor Pharmaceuticals, LLC

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0000	03/30/2018	All
0004	5/15/2018	Facilities
0005	5/18/2018	Drug Product
0010	7/20/2018	Biopharm
0014	9/28/2018	Drug Product
0015	10/26/2018	Drug Product
0016	11/21/2018	Drug Product
0017	11/29/2018	Biopharm

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Andrei Ponta	Wendy Wilson-Lee
Drug Product	Andrei Ponta	Wendy Wilson-Lee
Process/ Microbiology	Hang Guo	Derek Smith
Facility	Hang Guo	Derek Smith
Biopharmaceutics	Parnali Chatterjee	Ta-Chen Wu
Regulatory Business Process Manager	Teshara G. Bouie	
Application Technical Lead	David Claffey	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Acceptable	27-Jan-2017	
	II		Acceptable	DEC 2018	Found acceptable by both drug product and process review teams.	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	124019	
ANDA	200166	

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend approval from a product quality perspective. The drug substance and drug product information were referenced to DMFs (b) (4), respectively. Both were found adequate to support this application.

II. Summary of Quality Assessments

A. Product Overview

The drug substance is amphetamine sulfate 1:1 racemic mixture. The dosage form is an immediate release orally disintegrating tablet (ODT) in (b) (4) strengths: 5 mg, 10 mg, 15 mg, 20 mg, (b) (4) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years and older. Patients are directed to take one dose on awakening, with additional doses (one or two) at intervals of four to six hours. The recommended maximum daily dose is 40 mg.

The drug product is a white to off-white, round, flat faced, radius edged tablet with the strength (e.g. “5”) debossed on one side and “EVI” on the other. The lower strengths (5 mg, 10 mg, 15 mg) are packaged in 30-count blisters while the larger strengths (20 mg, (b) (4)) are packaged in 15-count blisters. The drug product can be stored at controlled room temperature. The applicant’s proposed a 24-month expiry was found to be acceptable.

(b) (4)

Proposed Indication(s) including Intended Patient Population	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years and older.
Duration of Treatment	Chronic
Maximum Daily Dose	40 mg

B. Quality Assessment Overview

(b) (4)

DRUG SUBSTANCE: The drug substance is amphetamine sulfate 1:1 racemic mixture. It is a compendial and the drug substance specification meets the USP monograph with (b) (4) % limits for individual impurities. Details are cross referenced to DMF (b) (4) which was last reviewed on 27-Jan-2017 and was found adequate to support an ANDA. There have been no other updates to the DMF since the last review. The DMF is currently active and found adequate to support this application.

DRUG PRODUCT: The dosage form is an immediate release orally disintegrating tablet (ODT) in (b) (4) strengths: 5 mg, 10 mg, 15 mg, 20 mg, (b) (4). The tablets are white to off-white, round, flat faced, radius edged tablet with the strength (e.g. "5") debossed on one side and "EVI" on the other. The lower strengths (5 mg, 10 mg, 15 mg) are packaged in 30-count blisters while the larger strengths (20 mg, (b) (4)) are packaged in 15-count blisters. The blister pack is packaged into (b) (4).

The drug product is to be stored at controlled room temperature. The applicant's proposed a 24-month expiry period was found to be acceptable.

Much of the drug product information was cross -referenced to DMF (b) (4). The bulk drug product manufacturing, drug product release testing, and drug product stability testing is performed by the DMF holder, (b) (4). (b) (4) performs the final drug product packaging and labeling.

Excipients include mannitol, ethyl cellulose, amino methacrylate copolymer, dibutyl sebacate, magnesium stearate, silicified microcrystalline cellulose, crospovidone, citric acid anhydrous, malic acid, sucralose, and (b) (4).

The drug product specification is typical and includes a test for disintegration at the (b) (4) limit recommended by the ODT Guidance. It also included strength-specific tablet hardness acceptance ranges.

Stability data support the proposed 24-month expiry when stored at controlled room temperature.

A categorical exclusion claim for submission of an environmental assessment based on 21 CFR §25.31(b) was found acceptable.

Process: Refer to Review #1 for DMF (b) (4) This was found adequate from a process review perspective. The manufacturing and testing sites were found acceptable by OPF.

Biopharm: Although the proposed dissolution method was found to have limited discriminating ability to detect formulation and manufacturing process changes, the biopharm review team found it adequate to control the quality of the proposed drug product. On Agency request the applicant agreed (b) (4) the dissolution acceptance criterion to 'Q = (b) (4) % in 15 minutes.

FDA' Approved Dissolution Method and Acceptance Criterion for

Eyekeo (amphetamine sulfate) ODT™, 5, 10, 15, 20, (b) (4)

Apparatus/Speed	USP Apparatus 2 (paddle)/ 50 rpm
Volume/Media/Temp	900 ml HCl 0.1 N at 37.0±0.5°
Acceptance Criterion	Q = ^(b) ₍₄₎ % at 15 minutes

In vitro dissolution data fully support the bridging between the clinical and the commercial products (b) (4)

Biowaiver Request for Lower and Higher Strengths: This submission included a BA/BE waiver request for the proposed lower 5 mg, 10 mg, 15 mg strengths (b) (4) not evaluated in PK/clinical studies. The totality of evidence provided supported the biowaiver request for the 5 mg, 10 mg, 15 mg, (b) (4) strengths.

From the Biopharmaceutics perspective, the risk of the proposed drug product on failing dissolution is low because the drug substance, amphetamine sulfate, exhibits high aqueous solubility across the physiological pH range 1.2-6.8 (b) (4)

C. Special Product Quality Labeling Recommendations (NDA only)

None.

D. Final Risk Assessment (see Attachment)



David
Claffey

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LABELING

I. Package Insert



(b) (4)

1. Highlights of Prescribing Information

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	EVEKEO ODT (amphetamine sulfate orally disintegrating tablets)
Dosage form, route of administration	Tablets, oral
Controlled drug substance symbol	CII
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Orally Disintegrating Tablets: 5 mg, 10 mg, 15 mg, 20 mg, (b) (4)

Is the information accurate? Yes No

2. Section 2 Dosage and Administration

2.3 Administration Instructions

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	The drug product is an orally disintegrating tablet and should be placed on the tongue and allowed to disintegrate.

Is the information accurate? Yes No

3. Section 3 Dosage Forms and Strengths

3 DOSAGE FORMS AND STRENGTHS

Evekeo ODT (amphetamine sulfate orally disintegrating tablets) are supplied as follows:

- 5 mg: white to off-white, round, flat-faced radius-edged tablet with “5” on one side and “EVI” on the other,
- 10 mg: white to off-white, round, flat-faced radius-edged tablet with “10” on one side and “EVI” on the other.
- 15 mg: white to off-white, round, flat-faced radius-edged tablet with “15” on one side and “EVI” on the other.
- 20 mg: white to off-white, round, flat-faced radius-edged tablet with “20” on one side and “EVI” on the other.

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Orally Disintegrating Tablets
Strengths: in metric system	5 mg, 10 mg, 15 mg, 20 mg, (b) (4)
Active moiety expression of strength with equivalence statement	Amphetamine Sulfate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	White to off-white, round, flat faced, radius edged tablet with the following description: 5 mg: “5” on one side and “EVI” on the other 10 mg: “10” on one side and “EVI” on the other 15 mg: “15” on one side and “EVI” on the other 20 mg: “20” on one side and “EVI” on the other (b) (4)

Is the information accurate? Yes No

4. Section 11 Description

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	EVEKEO ODT (amphetamine sulfate orally disintegrating tablets)
Dosage form and route of administration	Orally Disintegrating Tablets: 5 mg, 10 mg, 15 mg, 20 mg, (b) (4)
Active moiety expression of strength with equivalence statement (if applicable)	Amphetamine Sulfate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Mannitol, ethyl cellulose, amino methacrylate copolymer, dibutyl sebacate, magnesium stearate, silicified microcrystalline cellulose, crospovidone, citric acid anhydrous, malic acid, sucralose
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	A central nervous system stimulant
Chemical name, structural formula, molecular weight	(C ₉ H ₁₃ N) ₂ • H ₂ SO ₄ - 368.49 g/mol
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	pH of 5 to 8 in solution and is freely soluble in water, slightly soluble in alcohol and practically insoluble in ether

Is the information accurate? Yes No

5. Section 16 How Supplied/Storage and Handling

EVEKEO ODT is supplied as follows:



(b) (4)

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C -30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Store EVEKEO ODT blister packages in the provided (b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Orally Disintegrating Tablets: 5 mg, 10 mg, 15 mg, 20 mg, (b) (4)
Available units (e.g., bottles of 100 tablets)	Amphetamine Sulfate IR ODT are packaged in 15-count (20, (b) (4) mg strengths) and 30-count (5, 10, and 15 mg strengths) blister packs of the same strength with one individual tablet in each cavity
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White to off-white, round, flat faced, radius edged tablet with the following description: 5 mg: "5" on one side and "EVI" on the other 10 mg: "10" on one side and "EVI" on the other 15 mg: "15" on one side and "EVI" on the other 20 mg: "20" on one side and "EVI" on the other (b) (4)
Special handling (e.g., protect from light)	Not Applicable
Storage conditions	USP controlled room temperature
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Arbor Pharmaceuticals, LLC

Reviewer’s Assessment of Package Insert: Adequate
 Prescribing Information complies with all regulatory requirements from a CMC perspective.

II. Labels:

1. *Container and Carton Labels*

(b) (4)



(b) (4)

**2. Carton Label**



Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)))	EVEKEO ODT (amphetamine sulfate orally disintegrating tablets) Reviewer's Note: Applicant will be asked to remove (b) (4) from the name	EVEKEO ODT (amphetamine sulfate orally disintegrating tablets) Reviewer's Note: Applicant will be asked to remove (b) (4) from the name
Dosage strength	Complies	Complies
Net contents	Complies	Complies
"Rx only" displayed prominently on the main panel	Complies	Complies
NDC number (21 CFR 207.35(b)(3)(i))	Complies	Complies
Lot number and expiration date (21 CFR 201.17)	Complies	Complies
Storage conditions	Complies	Complies
Bar code (21CFR 201.25)	Complies	Complies
Name of manufacturer/distributor	Arbor Pharmacueticals, LLC	Arbor Pharmacueticals, LLC
And others, if space is available	Not Applicable	Not Applicable

Reviewer's Assessment of Labels: Adequate

The carton/container label complies with regulatory requirements from a CMC perspective, with the exception of the proprietary name. It bears the "Rx only" statement, the NDC number, name of manufacturer, lot number, expiration date, net contents, bar code, strength, and the name (proprietary and established).

Revisions identified and will be communicated to the Applicant as part of DPP labeling negotiations. The carton/container labeling is adequate assuming Applicant accepts edits.

List of Suggested Edits Communicated to Applicant:

1. Remove (b) (4) from the proprietary name in the carton, (b) (4), and blister labelin.

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name and Date: Andrei Ponta, Ph.D. 13-Sep-2018



Andrei
Ponta

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Wendy
Wilson- Lee

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Date: 12/04/2018 03:05:07PM
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BIOPHARMACEUTICS

NDA: 209905

Drug Product Name / Strength: Evekeo (amphetamine sulfate) ODT™

Immediate Release Orally Disintegrating Tablets, 5 mg, 10 mg, 15 mg, 20 mg, (b) (4)

Route of Administration: Oral

Applicant Name: Arbor Pharmaceuticals, LLC.

Primary Reviewer: Parnali Chatterjee, Ph.D.

Secondary Reviewers: Ta-Chen Wu, Ph.D./**Tertiary Reviewer:** Angelica Dorantes, Ph.D.

REVIEW SUMMARY:

Background This 505(b)(2) NDA application relies on FDA's previous findings of safety and effectiveness for the Listed Drug product for Amphetamine Sulfate Tablets under NDA 83901 approved in August 1984, sponsored by Lannett. However, because Lannett's Listed Drug product is discontinued, FDA in 2015 allowed the Applicant to establish the bridge to NDA 83901, by a comparative bioavailability study between the proposed Evekeo ODT product and Evekeo IR Tablets (Reference Standard, ANDA 200166, approved on August 2012).

In the current submission, the Applicant is seeking approval for immediate-release (IR), orally disintegrating tablets (ODT) containing 5 mg, 10 mg, 15 mg, 20 mg, (b) (4) of single amphetamine sulfate salt to be administered orally once daily for the treatment of attention deficit hyperactivity disorder (ADHD). The proposed product was developed as a line extension to Arbor's amphetamine sulfate immediate release 5 mg and 10 mg Evekeo Tablets.

The overall clinical development program is based on the comparative bioavailability study AR17.001, evaluating the equivalence of Evekeo IR ODT to Evekeo IR Tablets and study AR17.002, evaluating the effect of food on Evekeo ODT.

Review: The objective of the Biopharmaceutics Review was the evaluation of the information/data supporting the approval of the following; **1)** the proposed dissolution method and acceptance criterion, **2)** bridging of the proposed drug product throughout development, and **3)** biowaiver request for the lower 5 mg, 10 mg, 15 mg (b) (4) strengths not evaluated in PK/clinical studies.

Assessment: Based on the review of the provided information/data, Biopharmaceutics has the following comments and recommendations:

- **Dissolution Method and Acceptance Criterion:** Although the proposed dissolution method has limited discriminating ability to detect formulation and manufacturing process changes, this Reviewer considers that the method is adequate to control the quality of the proposed (b) (4) µg product and is acceptable. However, the proposed dissolution acceptance criterion of 'Q= (b) (4)% in (b) (4) minutes' is permissive and therefore, the Applicant was requested (b) (4). On Nov 29, 2018, the Applicant responded to the FDA's request and agreed to implement the FDA's



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recommended dissolution acceptance criterion of 'Q = (b) (4)% in 15 minutes. The table below describes the final approved dissolution test to be used for all the strength of the proposed drug product at release and on stability.

FDA' Approved Dissolution Method and Acceptance Criterion for Evekeo (amphetamine sulfate) ODT™, 5, 10, 15, 20, (b) (4)	
Apparatus/Speed	USP Apparatus 2 (paddle)/ 50 rpm
Volume/Media/Temp	900 ml HCl 0.1 N at 37.0±0.5°
Acceptance Criterion	Q = (b) (4)% at 15 minutes

➤ **Bridging Throughout Product Development:** All the strengths of the proposed drug product are manufactured (b) (4)



In conclusion, the overall in vitro dissolution data fully support the bridging between the clinical and the commercial products.

➤ **Biowaiver Request for Lower and Higher Strengths:** This submission included a BA/BE waiver request for the proposed lower 5 mg, 10 mg, 15 mg strengths (b) (4)

The provided information/data fulfills the biowaiver requirements regarding; (i) acceptable BA/BE data for the 20 mg strength product (ii) formulation compositional proportionality among all the strengths, (iii) dissolution profile comparison data between the 20 mg (BE-reference) and each of the other strengths(test) (b) (4)

(b) (4), and (iv) PK linearity over the 5 mg- (b) (4) mg dose range.

In conclusion, based on the totality of evidence the biowaiver request for the 5 mg, 10 mg, 15 mg, (b) (4) is GRANTED.

➤ **Biopharmaceutics Risk Assessment:** From the Biopharmaceutics perspective, the risk of the proposed drug product on failing dissolution is low because the drug substance, amphetamine sulfate, exhibits high aqueous solubility across the physiological pH range 1.2-6.8 (b) (4)



OVERALL REVIEW RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 209905 for Evekeo (amphetamine sulfate) ODT™, 5 mg, 10 mg, 15 mg, 20 mg, (b) (4) is recommended for **APPROVAL**.

(b) (4)

Table 3. Amphetamine Sulfate ^{(b) (4)} Formulations A, B, and C

Component	% Weight		
	A	B	C
Mannitol USP	^{(b) (4)}		
Amphetamine Sulfate USP			
Ethylcellulose NF			

(b) (4)



➤ **MANUFACTURING SITES FOR THE PROPOSED DRUG PRODUCT:**

The Applicant identified [REDACTED] (b) (4) as the manufacturing, stability, and finished product release testing site for the commercial drug product, including dissolution testing. The Applicant also identified [REDACTED] (b) (4) as the packaging and labelling site for the finished final drug product.

➤ **BCS DESIGNATION**

Amphetamine sulfate is reported in the literature as a BCS [REDACTED] (b) (4) drug substance. However, it is noted that the proposed drug product is out of the purview of the BCS Guidance because it is absorbed in the oral cavity.

- Solubility:** Amphetamine sulfate, USP, exhibits high aqueous solubility. The equilibrium solubility of the drug substance was determined in buffer solutions across the physiological pH range 1.2-6.8 for 24 hours at 37°C as shown in **Table 5** (refer to: [\\cdsesub1\evsprod\mf \(b\) \(4\) 0001\m3\32-body-data\32p-drug-prod\amphetamine-sulfate-\32p2-pharm-dev\pharmaceutical-development1.pdf](\\cdsesub1\evsprod\mf (b) (4) 0001\m3\32-body-data\32p-drug-prod\amphetamine-sulfate-\32p2-pharm-dev\pharmaceutical-development1.pdf)). It should be noted that 0.1 M citric acid and 0.2 M dibasic sodium phosphate were used to prepare pH 3.6-6.6 buffer solutions.

Table 5. Solubility Profile of Amphetamine sulfate in Buffer Solutions pH 1.2-6.8 at 37 C

Solvent	Starting pH	Ending pH	Solubility (mg/mL)
0.1N HCl	1.25	1.93	102.95
0.1M Citric acid	2.10	2.53	101.13
pH 3.6 buffer	3.60	3.56	102.03
pH 5.0 buffer	5.00	4.93	94.31
pH 6.6 buffer	6.60	6.41	95.09
0.2M Na ₂ HPO ₄	9.15	7.96	94.30

- Permeability:** In vivo/in vitro permeability studies were not provided in the application.

Reviewer’s Assessment of Drug Substance Solubility:

The highest proposed dose for amphetamine sulfate in the drug product is (b) (4). Accordingly, amphetamine sulfate can be classified as a highly soluble drug substance, as per BCS Guidance.

➤ **DISSOLUTION TESTING:**

Dissolution testing was identified as a critical quality attribute (CQA) for the proposed drug product due to the immediate-release (IR) orally disintegrating attribute of the drug product and is utilized to control the quality of the proposed drug product during development, for the batches used in the pivotal clinical PK studies, and for batches on stability. Dissolution testing was also used to select the final drug product formulation and final manufacturing process.

➤ **PROPOSED DISSOLUTION METHOD:**

The dissolution method and dissolution acceptance criterion proposed by the Applicant for the dissolution testing of the proposed drug product are shown below in **Table 6**.

Table 6. Proposed Dissolution Method and Acceptance Criterion for Evekeo (amphetamine sulfate) ODT™, 5 mg, 10 mg, 15 mg, 20 mg, (b) (4)

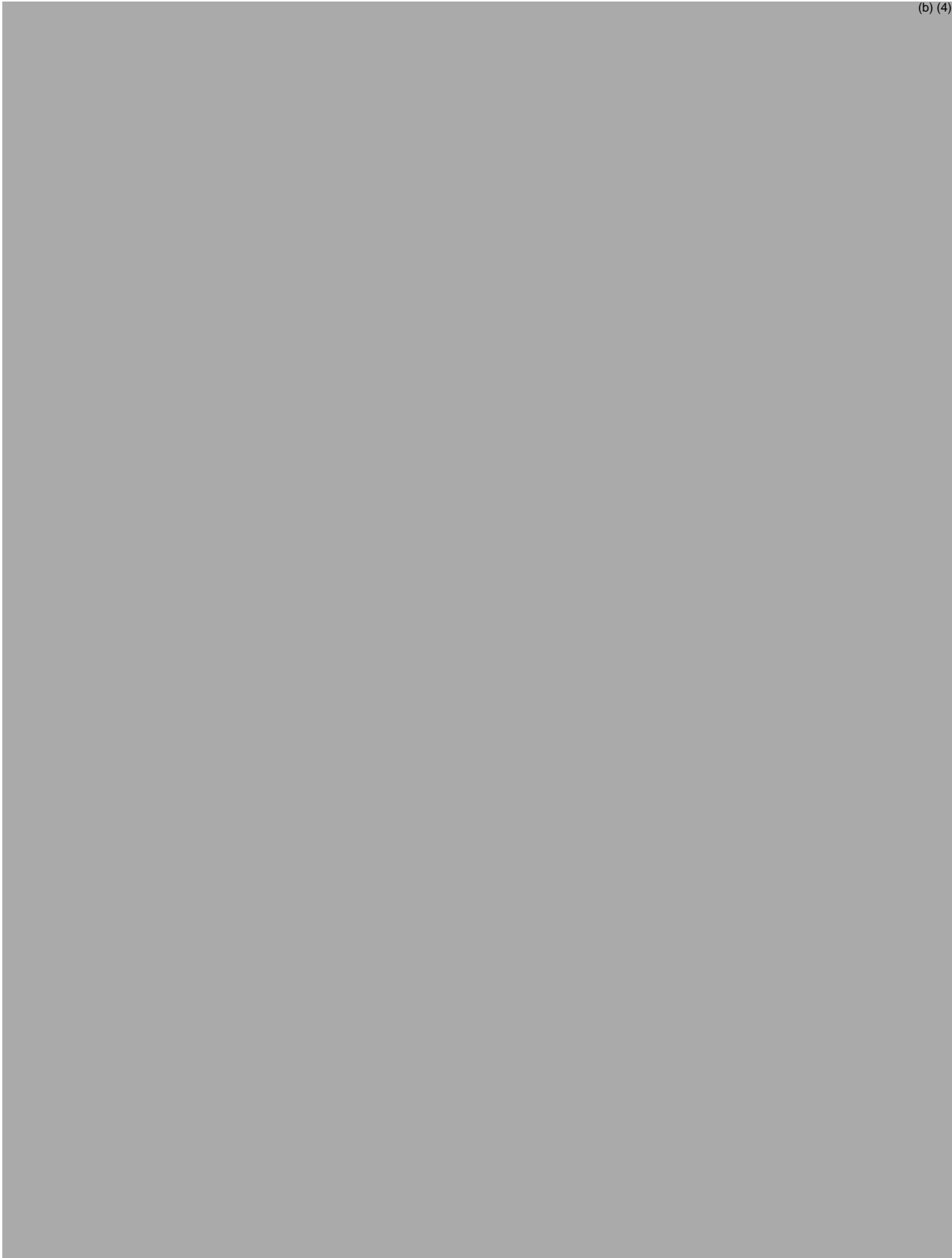
Parameters	Method
Apparatus/Speed	USP Apparatus 2 (paddle)/ 50 rpm
Media/Volume/Temperature	0.1 N HCl/900 mL/37.0±0.5 C
Dissolution Acceptance Criterion	‘Q= (b) (4)% in (b) (4) minutes’



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(b) (4)



It should be noted that sink condition will be achieved in 500 mL volume of the dissolution medium for the highest strength (b) (4) of the drug product because the drug substance is highly soluble in 0.1 N HCl (~100 mg/mL, see **Table 5**). However, the Applicant proposed 900 mL volume of the dissolution medium.

- **Discriminating Ability of the Proposed Dissolution Method:** (b) (4)

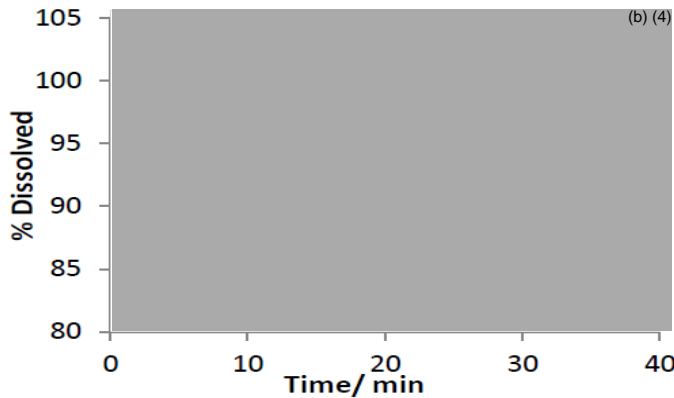


Figure 1. Dissolution Profile for Batches B, F (Target Batch), and H Manufactured with Process Variables

➤ ***PROPOSED DISSOLUTION ACCEPTANCE CRITERION:***

The Applicant proposed ‘Q= (b) (4)% in (b) (4) minutes’ as the dissolution acceptance criterion for batch release and stability testing of the proposed product, Evekeo (amphetamine sulfate) ODT™, 5 mg, 10 mg, 15 mg, 20 mg, (b) (4)





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(b) (4)



TEST PARAMETERS	ACCEPTANCE CRITERIA	RESULTS
4. Dissolution 900mL 0.1N HCl @ 37C USP 2 @ 50RPM	(b) (4)min: NLT (b) (4)% (Q).....	(b) (4)%

Reviewer's Assessment of Proposed Dissolution Method and Acceptance Criterion:

The proposed dissolution testing conditions regarding equipment, paddle rotation speed, dissolution medium are adequate. With respect to the Applicant's selected 900 ml volume, 500 ml will be a more optimal volume for the dissolution testing of this product; however, because the dissolution data for the bio-batch and registration stability batches were collected using 900 ml, this reviewer is willing to accept the proposed volume. Regarding the discriminating ability of the proposed method, because amphetamine sulfate exhibits high solubility across the physiological pH=1.2 to 6.4 range (b) (4), the proposed dissolution method has not ability to differentiate between batches with formulation and manufacturing process changes.

The provided dissolution data for the clinical and commercial batches of the proposed drug product (b) (4)

Therefore, the Applicant was recommended via an Information Request to implement Q= (b) (4)% in 15 minutes as the dissolution acceptance criterion for all the strengths of their proposed

drug product. In their response dated November 29, 2018, the Applicant agreed to implement the FDA's recommended dissolution acceptance criterion.

Table 9 summarizes the final approved dissolution test to be used for all the strength of the proposed drug product at release and on stability.

Table 9. FDA' Approved Dissolution Method and Acceptance Criterion for Evekeo (amphetamine sulfate) ODT™, 5, 10, 15, 20, (b) (4)	
Apparatus/Speed	USP Apparatus 2 (paddle)/ 50 rpm
Volume/Media/Temp	900 ml HCl 0.1 N at 37.0±0.5°
Acceptance Criterion	Q = (b) (4)% at 15 minutes

Additionally, it is noted that all the strengths of the proposed drug product met the NMT (b) (4) (b) (4) disintegration time acceptance criterion required for the disintegration test of an ODT dosage form.

➤ **Bridging of Formulations:**

All strengths of the proposed drug product are manufactured (b) (4) (b) (4). The blend for the commercial scale drug product is different than the blend used in the drug product that was administered in the clinical studies. (b) (4)

(b) (4) The qualitative and quantitative differences between the clinical formulation and commercial formulation are provided in **Table 10 a**.

Table 10a. Qualitative and Quantitative Differences between the Amphetamine Sulfate blends used for the Clinical and Commercial Formulations

Component	% Composition	
	Clinical Scale Formulation	Commercial Scale Formulation
Amphetamine Sulfate (b) (4)	(b) (4)	
Mannitol (b) (4)		
Silicified Microcrystalline Cellulose NF		
Crospovidone NF		
Citric Acid Anhydrous USP		
Malic Acid NF		
Sucralose NF		
(b) (4)		

The dissolution profile data for six commercial batches exhibits > (b) (4)% release of amphetamine in 15 minutes (see **Table 10b**), (b) (4)

Reviewer's Assessment for Bridging:

The overall in vitro dissolution data fully support the bridging between the clinical and the commercial products.

➤ *Biowaiver Request for Lower and Higher Strengths:*

This submission includes the Applicant's request for a 'waiver' of the requirement for the submission of in vivo bioavailability data for the lower 5 mg, 10 mg, 15 mg strengths (b) (4) of the proposed drug product not tested in PK/clinical studies. To fulfill the Biowaiver request requirements, the Applicant provided the following; (i) in vivo BA/BE data for the 20 mg strength drug product, (ii) PK linearity information for the proposed 5mg (b) (4) mg dosing range, (iii) formulation-compositional proportionality of all proposed strengths, and (iv) in vitro dissolution profile comparison data for all strengths of the proposed drug product in multi-pH media.

Specifically, to support the biowaiver for the 5 mg, 10 mg, 15 mg, (b) (4) strengths of the proposed drug product, the Applicant provided:

1. Study AR17.001, an in vivo BA/BE study conducted with a single 20 mg strength bio-batch (Lot No. PF59310001,) with and without water, vs. two×10 mg Evekeo™ IR reference standard (RS) tablets with water under fasting conditions. The study results support the bioequivalence between the 20 mg strength and two×10 mg Evekeo™ Tablets (reference Standard). It is noted that the evaluation of study, AR17.001 was performed by

the Office of Clinical Pharmacology and the ClinParm Reviewer, Dr. Kofi Kumi indicated that BA/BE study AR17.001 is acceptable.

2. Information demonstrating that the formulations (active and inactive ingredients) of the 5 mg, 10 mg, 15 mg, (b) (4) strengths of the proposed drug product are qualitatively and quantitatively proportional to the 20 mg bio-strength;
3. The 5 mg, 10 mg, 15 mg, (b) (4) strengths of the drug product (b) (4)
(b) (4)
4. Information demonstrating dose linearity over the proposed 5 to (b) (4) mg range was provided

Reviewer's Assessment for Biowaiver Request of Lower and Higher Strengths:

*The provided information/data fulfills the biowaiver requirements regarding; (i) acceptable BA/BE data for the 20 mg strength product (ii) formulation compositional proportionality among all the strengths, (iii) dissolution profile comparison data between the 20 mg (BE-reference) and each of the other strengths(test) (b) (4)
(b) (4) and (iv) PK linearity over the 5 mg (b) (4) dose range. Based on the totality of evidence the biowaiver request for the 5 mg, 10 mg, 15 mg, (b) (4) strengths is GRANTED.*

➤ **BIOPHARMACEUTICS RISK ASSESSMENT:**

Because amphetamine sulfate exhibits a high solubility profile across the physiological pH 1.2-6.4 range and the proposed drug product is (b) (4)
(b) (4) from the Biopharmaceutics perspective the risk of failing the dissolution test is very low.

➤ **OVERALL REVIEW RECOMMENDATION:**

From the Biopharmaceutics perspective, NDA 209905 for Evekeo (amphetamine sulfate) ODT™, 5 mg, 10 mg, 15 mg, 20 mg, (b) (4) strengths is recommended for **APPROVAL**.

➤ **POST-APPROVAL COMMITMENTS: None**



Ta-Chen
Wu

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Angelica
Dorantes

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, stability (impurities/degradation products)		L	(b) (4)	Acceptable	
Content Uniformity		M		Acceptable	
Microbial limits		L		Acceptable	
Physical Stability		L		Acceptable	
Scored: friability		M		Acceptable	
Scored: CU		M		Acceptable	
Dissolution		L		Acceptable	
Disintegration		L		Acceptable	
(b) (4)		M		Acceptable	



David
Claffey

Digitally signed by David Claffey

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